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JOHN E. BURKE
GREENBERG TRAURIG LLP
1200 17TH STREET, SUITE 2400
DENVER, CO 80202

| EXAMINER | |
|---|---|
| BERTOGLIO, VALARIE E | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/892,206 | BRENNAN ET AL. | |
| | Examiner | Art Unit | |
| | Valarie Bertoglio | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34-37,41 and 43-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37,41,43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed 06/24/2005 has been received. Claims 34-37,41,43,46 and 48 have been amended. Claims 1-33,38-40 and 42 have been cancelled. Claims 34-37,41,43-48 are pending and under consideration in the instant office action.

### *Priority*

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, US Provisional Application 60/215,467, filed 06/29/2000 and US Provisional Application 60/244,083, filed 10/26/2000, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of these applications as set forth in the utility and enablement rejections for the instant application that is under examination.

The instant application claims priority to two provisional applications. Support for the phenotypes of claims 34-36 of the instant application cannot be found in the parent application 60/215,467, filed 06/29/2000 and support for the phenotypes of claims 34 and 36 of the instant application cannot be found in the parent application 60/244,083, filed 10/26/2000. Specifically, the instant specification teaches the claimed mice exhibit reduced thymus size, lower dose of metrazol to reach seizure and a decrease in prepulse inhibition at 90dB. Only the phenotype of lower dose of metrazol to reach seizure and increased susceptibility are taught by 60/244,0863, filed 10/26/2000. In as much as claims 34-36 and 48 are considered to introduce new matter into the instant application (see below), support for these claims is not found in the provisional applications either.

Therefore, priority is denied on two grounds. Claims 34-36 and 48 are denied priority to 60/215,467, filed 06/29/2000 and claims 34,36 and 48 are denied priority to 60/244,083, filed 10/26/2000 for the reasons set forth above regarding lack of support for the claimed phenotypes in the priority document. Furthermore, all claims 34-37,41 and 43-48 are denied priority to either document as they are not enabled by specification of the instant application and do not meet the requirements of 35 USC 101/112 pertaining to use of the claimed invention. Accordingly, all pending claims are granted an effective filing date of 06/26/2001.

***Specification***

The amendment filed 06/24/2005 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant has amended the specification at page 11, paragraph 3 to incorporate US Provisional Application 60/084194. This reference is not considered new matter because the original specification incorporated USSN 08/971310 by reference, which was converted to the Provisional Application 60/084194. However, the additional references are considered new matter. The references include a second provisional application (60/084949), a utility application claiming priority to the two provisional applications (09/193,834) and a second utility application that is a continuation of the first utility application (09/885,816; published as US Patent 6,815,185). There is no evidence that these newly referenced applications were contemplated as being part of the original specification as an incorporation by reference. The reference to "U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent Application No. 09/885,816, filed June 19, 2001, which is a continuation of U.S. Patent Application No. 09/193,834, filed November 17, 1998, now abandoned, which claims priority to provisional application no. 60/084,949, filed on May 11, 1998, and provisional application no. 60/084,194, the disclosure of provisional application no. 60/084,194" should be replaced with "US Patent Application No. 08/971,310, which was converted to provisional application no. 60/084194". The other applications should not be included.

***Claim Objections***

The objection to claim 41 is maintained for reasons of record set forth at page 2 of the office action mailed 02/15/2005. Applicant's arguments have been considered and are not persuasive.

Applicant has traversed the objection of claim 41 regarding the recitation that a pseudopregnant mouse gives birth. Applicant refers to a published textbook setting using the

terminology and asserts that the terminology would be clearly understood by one skilled in the art (see page 5, paragraph 4 of Applicant's Remarks). In response, the objection is maintained. Upon impregnation, the pseudopregnant mouse of the claim is no longer pseudopregnant. The clarity of references to pseudopregnant mice in a textbook has little weight in establishing that it is accepted in the art to call a pregnant mouse pseudopregnant. For the sake of clarity, Applicant should amend the claim to read "wherein the resulting pregnant mouse gives birth to a chimeric mouse".

Claim 47 is objected to because of the following informalities: Claim 47 recites the terminology "neomycin resistant gene". Genes do not exhibit resistance to an antibiotic. However, they can encode antibiotic resistance. Therefore, this terminology should be replace with "neomycin resistance gene" or "gene encoding neomycin resistance". Appropriate correction is required.

### *Claim Rejections - 35 USC § 101/112*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Utility*

Claims 34-37,41 and 43-48 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The rejection set forth on pages 2-7 of the previous office action mailed

02/15/2005 is maintained for reasons of record. Applicants arguments filed 06/24/2005 have been fully considered and are not persuasive.

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf ]

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

See also the MPEP § 2107 - 2107.02.

The instant specification has discussed that the mice of the instant invention can be used as models of disease to screen for drug therapies and as a tool for studying the function of a gene encoding SEQ ID NO:1. As set forth in the previous office action, these uses fail to meet the standards of a specific, substantial and well-established utility required under 35 U.S.C. 101. In summary, the utilities provided by Applicant for the claimed mouse are not specific or substantial and therefore are not well established because the use of the mouse in screening for drugs to treat an unknown disease is not specific or substantial. The use for the claimed mouse in

characterizing the function of a gene encoding SEQ ID NO:1 is not substantial. The teachings in the specification failed to characterize or define the role of the gene that correlates to the cDNA set forth by SEQ ID NO:1. Therefore, it cannot be determined without additional experimentation that the claimed gene and knockout mouse has a well-established use. The skilled artisan would not know how to use a mouse that exhibits the claimed phenotypes other than for further study of that mouse to determine a real world use. Further basis for this rejection is further set forth in the previous office action dated 02/15/20054 and in the guidelines above.

Applicant has argued that the Patent Office guidelines state that a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose (pages 6-11). Applicant cites excerpts from an NIH website, Austin et al., 2004, Lewin's Genes VII, and others (pages 8-11 of Applicant's response) in establishing that knockout mice are invaluable tools of scientific research. Applicant also cites the MPEP in discussing the utility of research tools (pages 9-10 of Applicant's response; MPEP 2107.01, I). Applicant cites Langer to support the argument that the assertion of a utility is credible unless the logic underlying the assertion is flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (page 6). Applicant maintains that rejections under 35 USC 101 have rarely been sustained by the federal courts (page 7, top). In general, Applicant does not understand how the invention cannot have utility when the invention is being used by one of skill in the art and has clearly been accepted as useful by several leaders in the field of transgenic technology.

In response, the instant invention has failed to meet the requirements of possessing a well-established utility and for a use with any particular practical purpose. A well-established

utility and a utility with a particular practical purpose is one that is specific and substantial (see MPEP 2107(II)(A)(3)(ii) and MPEP 2107 (II)(B)(1)). The utility of the instant invention is neither specific nor substantial for reasons of record. Applicant is reminded that the utility guidelines (see above) expressly state that utilities requiring further research to identify or reasonably confirm a use do not define substantial utilities. Examples of uses that are not considered substantial utilities include basic research in studying the claimed product and use to screen for therapeutics for an unspecified disease. The use of the invention by the skilled artisan does not impart patentability or patentable use on the invention for reasons set forth above.

With specific respect to Applicant's applied references, the validity of the opinion of the NIH, Ben Lewin, Austin et al. and others with respect to the value of the knockout mouse in determining gene function is not questioned. However, the use of a mouse to determine gene function, as set forth above, does not meet the requirement that a utility be specific and substantial, and therefore, does not fulfill the requirements of utility under 35 USC 101. With respect to MPEP 2107.01, I, a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph.

Finally, the credibility of the alleged general use for elucidating gene function is not the basis of the rejection. While it may be credible that the mouse can be used to study gene function, such a use is neither specific nor substantial as set forth in the previous office action.

Furthermore, whether the federal courts have sustained other rejections under 35 USC 101 does not make the instant rejection improper and Applicant's argument is not effective in persuading the withdrawal of the rejection. Therefore, the utility of the instant invention is neither specific nor substantial.

Applicant argues that the person of ordinary skill in the art would find the claimed invention useful for determining gene function (see pages 11-12 of Applicant's remarks).

In response, such a use is neither specific nor substantial as set forth in the previous office action. To use the claimed mouse to study gene function amounts to no more than study of the invention itself. Further experimentation is required to determine that this use has real-world utility. Furthermore, use of the claimed knockout mouse to study gene function is not specific in that any knockout mouse can be used to study the function of the gene knocked out or any other gene. Furthermore, there is no evidence that the claimed mouse will provide insight into the function of the anaphylatoxin C3a receptor gene because not all knockout mice are effective in revealing gene function. Merely knocking out a gene is not sufficient to confer specific utility on a mouse.

Applicant argues that the claimed invention has substantial utility (pages 12-14). Applicant asserts that further research is not required to identify any use. A use can be found for any mouse. For example, a knockout mouse with a disruption in a transcriptionally silent gene with no phenotype at all can be used as snake food. This is not a real-world use and does not overcome the requirement for specific and substantial utility. Likewise, the lack of a real world use for the claimed invention and the necessity for addition research to identify or confirm such a

use necessitates the rejection of the claimed invention as lacking substantial, and therefore, patentable utility.

Applicant has requested that the basis of the rejection be explained as it relates to "specific utility" (page 12). In response, the use of the claimed mouse to study the function of the anaphylatoxin C3a receptor gene is not specific because any particular knockout mouse can be used to study the particular gene that has been knocked out. This is a general utility and is not specific. Furthermore, there is no evidence that the claimed mouse will provide insight into the function of the anaphylatoxin C3a receptor gene because not all knockout mice are effective in revealing gene function. Merely knocking out a gene is not sufficient to confer specific utility on a mouse.

Applicant argues that the expression of *lacZ* in the claimed mouse provides specific utility (page 12). Again, the utility of this mouse is not specific in that any mouse constructed with a *lacZ* gene inserted into any gene, can be used to the same extent as the claimed mouse to study expression of the disrupted gene. Applicant has taught no specific properties of this mouse to set forth any real-world use. Basic research, study of the invention itself, and further research to confirm a real-world use are not patentable utilities (see above).

Applicant also discloses the commercial use of the claimed mice and states that commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art (page 14 of Applicant's remarks). Applicant has submitted a declaration from Dr. Robert Driscoll stating that the mice have been sold to at least one large pharmaceutical company for the use of studying gene function and for human therapeutic drug development.

In response, the commercial use of the claimed mouse is not dispositive of the lack of a specific and substantial asserted utility in the original specification and does not provide evidence of a well-established use at the time the application was filed. Paragraph 4 of the declaration states that mice obtained from Deltagen are used for study of gene function and human therapeutic drug development. The declaration does not state that the claimed mouse is being used for any particular purpose. Despite this, as set forth above and in the previous office action mailed 02/15/2005, uses in study of gene function and human therapeutic drug development for an unspecified disease, are not specific or substantial. Applicant is reminded that the requirements under §101 and §112, 1st para. must be met at the time the application is filed. There is no evidence in the declaration that the companies are using the mouse for any use identified in the specification. The discovery of an undisclosed use meeting these requirements after the application is filed does not satisfy the statutory requirements under either §101 or §112, 1st para. See *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967); *In re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993). The declaration filed does not provide any evidence that the requirements of a specific and substantial use were met at the time of filing.

Applicant questions why the claimed mouse is not a tool useful in identifying agonists of the anaphylatoxin C3a receptor gene (page 15).

In response, the mouse may well have a productive use in identifying agonists of anaphylatoxin C3a receptor. However, the specification discloses no use for such an agonist that is specific or substantial. Therefore, use of the mouse to identify the agent is neither specific nor substantial.

Applicant has referred to the principles set forth in *In re Brana* (see pages 15-17 of Applicant's remarks). Applicant asserts that the specification supports a use of the knockout mouse that is specific and substantial in light of the teaching of *In re Brana.*

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention.

*Enablement*

Claims 34-37,41 and 43-48 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 34-37,41 and 43-48 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. In addition to the reasons raised in the rejection made under 35 USC 101 for the specification failing to teach to use the claimed products and methods of making the claimed products, the claims further lack enablement for reasons set forth in the office action dated 02/15/2005 at pages 7-11 and reiterated below.

Applicants' arguments filed 06/24/2005 have been fully considered and are not persuasive.

1) Claims were previously rejected because the claims encompass mice that fail to exhibit any particular phenotype, which is not enabled.

Applicant argues that the claim recites that the allele is a null allele and that any null allele should result in the same phenotype, overcoming the necessity for a phenotypic limitation in the claims (see page 19 of Applicant's Remarks).

In response, the claims are broad and are not limited to the specific mice taught in the specification. The specification teaches how to make a mouse with a null anaphylatoxin C3a receptor allele exhibiting a particular list of phenotypes. The claims are more broad in scope and encompass phenotypes not disclosed in the specification. The specification does not teach how to make the claimed mouse exhibiting any phenotypes other than a lower dose of metrazol to elicit seizure, decreased prepulse inhibition with a 90dB prepulse (page 54). The specification does not demonstrate a reduced thymus weight as only male mutant mice have a somewhat lower thymus weight and one of the three mice have a thymus that weighs more than one of the only two wild-type examples (page 53). The statistical significance of the data is not demonstrated. Therefore, it is not even clear from the data presented that the mice even exhibit reduced thymus weight and

female mice appear to be normal in this respect based on the data shown. The specification does not teach how to make a mouse exhibiting any other phenotype as encompassed by 34,41 and 43-48). Other null alleles in the anaphylatoxin C3a receptor gene would be expected to result in the same phenotypes if the same genetic backgrounds are used (see Pearson, **Nature**, 415:8-9, 2002; Silva, **Neuron**, 19:755-759,1997) in making the mouse, as argued by Applicant, however, the other phenotypes encompassed by the claims, including the lack of a phenotype, would not be predicted or expected. By omitting a phenotypic limitation, the claims broadly encompass phenotypes not supported by the specification.

Therefore, one of skill in the art is not enabled by the specification or the art to make the transgenic mice broadly encompassed by the claims. The claims need phenotypic limitations that narrow the scope of what is being claimed to that which is described in the specification.

Examiner's comments regarding hypomorphic and hypermorphic alleles are withdrawn.

2) The aspect of the rejection pertaining to other anaphylatoxin C3a receptor genes is withdrawn in light of Applicant's arguments.

3) With respect to the breadth of the phenotypes claimed being greater than that supported by the specification, Applicant argues that there is no evidence to indicate that the claimed mice would not be more susceptible to seizure without metrazol administration. In response, the state of the art at the time of filing held that results obtained from seizure susceptibility studies are greatly affected by the genetic background of the mouse and might not be indicative of an epileptic disease state caused by the claimed disruption. For example, Schauwecker [**Progress in Brain Research**, 135:139-148, 2002] taught that there are complications associated with genetic models of epilepsy, specifically, for example, different

strains of mice vary in their response to chemically induced seizures (paragraph bridging pages 142-143; page 143; page 140, column 2, paragraph 2 and paragraph bridging pages 140-141). Royale also reported differences in seizure susceptibility in different inbred mouse strains [**Brain Research**, 816:337-349, 1999, specifically page 337, col. 2, page 345, section 3.2, page 347, 1st paragraph). Accordingly, it cannot be dismissed that the seizures induced at a lower dose of metrazol in mice comprising a disruption of the anaphylatoxin C3a gene is merely due to background differences between the mutant mice and control mice used in testing. Additional evidence indicating a state of epilepsy as opposed to a difference in test results based on genetic background difference is necessary to support the correlation Applicant is making between the observed chemically induced seizures and increased susceptibility to seizures, including spontaneous seizures as encompassed by the claims. Furthermore, it is noted that no data for evaluation of the degree or significance of the reported conclusions with respect to the phenotypes of the mice . Applicant merely provides a simple statement that there was an effect in the mutant mice.

Applicant has also argued that the mice exhibiting a decreased prepulse inhibition at 90dB is indicative that the mice exhibit a stimulus processing disorder. There is no support for such a correlation in the instant specification. The evidence of record fails to link the anaphylatoxin C3a receptor gene to a stimulatory processing disorder. Paylor et al [**Psycopharmacology**, 132:169-180, 1997] and Bullock et al [**Behavioral Neuroscience,** 111:1353-1360, 1997) have contrasted the startle responses of thirteen inbred (Paylor) and eight inbred (Bullock) mouse strains to investigate the potential genetic basis for differences in sensorimotor gating using the prepulse inhibition paradigm. It was found that some strains

showed high levels of prepulse inhibition while other strains showed low levels of prepulse inhibition. In light of the teachings of Paylor and of Bullock, the specification fails to provide a link between the disruption of the anaphylatoxin C3a receptor gene and the decreased prepulse inhibition observed in the claimed mice. Furthermore, it cannot be concluded that the claimed gene disruption is the cause for decrease prepulse inhibition at a single decibel level. The specification fails to disclose the genetic background of controls or to rule out the observed differences in prepulse inhibition as being normal differences resulting in differences in genetic background between the mutant and control mice.

Further data and characterization are necessary to make these phenotypic generalizations, and correlations to disorders, such as increased susceptibility to seizure under any condition or a stimulus processing disorder. Therefore, it would require undue experimentation to make the claimed mice exhibiting the phenotypes broadly encompassed by the claims.

*New Matter*

1) Claim 48 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The rejection as it relates to claims 43-47 is withdrawn in light of Applicants' amendments to claim 43.

Applicant's remarks have been fully considered but are not found persuasive as they relate to claim 48. The rejection of claim 43 is maintained for reasons of record set forth at pages 11-13 of the office action dated 02/15/2005.

Claim 43 has been amended to such that it no longer requires the presence of a visible marker. However, claim 48 continues to encompass a generic transgenic mouse comprising a neomycin resistance encoding gene and a lacZ gene. The specification does not provide support for the generic embodiments of the claim wherein the mouse, made using any genetic background and a lacZ gene. There is no general description of the claimed genera of mice comprising a selectable marker gene, including neomycin resistance, and lacZ. The specification describes only one species of mouse comprising the lacZ gene and that the claims are directed to some characteristics of the species while leaving out other characteristics of the species is new matter. For example, the only mouse described in the specification that comprises a lacZ gene was made using 129Sv-+P+Mgf-SLJ/J ES cells with the chimeric offspring outcrossed to C57BL/6. It appears that the lacZ was a promoterless lacZ placed upstream of the neomycin resistance gene. These limitations were omitted from the claim and are considered new matter as the use of lacZ was not generically taught in the specification and therefore was not described in any way other than in the context of these other specifications.

The specification does not describe a genus of knockout mice wherein the targeting construct contains a gene encoding lacZ. In contrast, the specification teaches, generically, that the targeting construct contains a positive selection marker between the targeting sequences. With respect to the lacZ gene, the specification does not mention, even in passing, a general feature of the claimed invention where the exogenous, inserted DNA encodes lacZ. Disclosure of

a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. See, for example, *In re Shokal*, 113 USPQ 283 (CCPA 1957); *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481 (CAFC 2000).

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

***Claim Rejections - 35 USC § 112-2nd paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 42, 46 and 47 under 35 USC 112, 2nd paragraph is withdrawn in light of Applicant's amendments to the claims.

***Claim Rejections - 35 USC § 102/103***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 34-37,41,43-47 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Humbles et al [**Nature**, 406:998-1001, August 2000] or Kildsgaard et al [**Jour Immunol**, 165:5406-5409, Nov 2000].

As set forth above, all claims are denied priority because the asserted priority documents do not meet the requirements of 35 USC 112 1st paragraph pertaining to enablement as established by the failure of the instant application to meet said requirements. Therefore, the claims have an effective filing date of June 26, 2001, which is after the publication date of Humbles et al. and Kildsgaard et al.

Both Humbles et al. and Kildsgaard et al taught transforming a mouse ES cell with a nucleic acid construct targeting the anaphylatoxin C3a receptor gene, resulting in an inactivating insertion of a selective marker gene, into the endogenous anaphylatoxin C3a receptor locus (Humbles, page 1000, col. 2, paragraph 3 and Figure 1; Kildsgaard, page 5406, col. 2, paragraph 4 and Figure 1), and using said cell to generate, by injection into a blastula, a mouse whose

genome comprises a disruption in the anaphylatoxin C3a receptor gene. The targeting construct comprised a neo resistance gene, which is a selectable marker (see Figure 1, both references). Humbles et al. and Kildsgaard et al. taught that the mutant allele is null by demonstrating that no full-length mRNA is produced (Humbles, Figure1B and 1C; Kildsgaard, page 5407, col. 2, paragraph 1 and Figure 1B and 1C). Humbles et al. and Kildsgaard et al. taught both heterozygous and homozygous mice. Humbles et al taught isolating bone marrow cells from the mice for analysis (Figure 1c, legend). Kildsgaard et al. taught cells or tissues isolated from the mice because blood containing cells was isolated for analysis (page 5407, column 1, paragraph 4).

Humbles et al. and Kildsgaard et al. did not explicitly teach the phenotypes of claims 34-36, however, the mouse of Humbles et al. and Kildsgaard et al. appears to be the same as that of the instant invention. Both mice have genomes comprising a null disruption of the same anaphylatoxin C3a receptor gene. Although the prior art did not measure and report the phenotypic aspects claims in claims 34-36, the mice appear to be the same. See MPEP 2112.01. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

2) Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Humbles et al. and Kildsgaard et al. as applied to claims 34-37,41,43-47 above, and further in view of Mansour [**Development**, 117:13-28 (1993)].

As set forth above, Humbles et al. and Kildsgaard et al. taught transgenic mice whose genome comprises an insertional disruption of the anaphylatoxin C3a receptor gene wherein the

inserted gene comprises a selectable neomycin resistance marker gene. Humbles et al. and Kildsgaard et al. did not teach the lacZ gene as part of the insertional disruption.

However, Mansour taught making transgenic knockout mouse wherein the insertional disruption included the lacZ gene. The targeting construct of Mansour comprised a visible lacZ marker gene (page 14, col. 1, paragraph 3) that was useful in staining mutant cells that would normally express int-2 (the gene knocked out) that could otherwise not be visualized by gene expression.

Accordingly, in view of the teachings of Humbles et al. and Kildsgaard et al. and of Mansour, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the knockout technology of Humbles et al. and Kildsgaard et al. by use of a targeting vector comprising the lacZ with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was routine in the art to disrupt a gene using a transgene comprising lacZ and doing so allows visualization of mutant cells that fail to express the endogenous gene as a result of the targeted insertion.

One would have a reasonable expectation of success in applying the technology of Mansour to the the knockout mouse of Humbles et al. and Kildsgaard et al. because it was routinely performed in the art and all sequences needed to carry out the invention were known.

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

3) The previous rejection of claims 42-48 under 35 USC 103(a) is withdrawn. Applicant has specified that the rejection of claims 1,3,4,16,20 and 21 is traversed. These claims are cancelled. However, Applicant's arguments have been considered as they relate to claims 42-48 that were rejected under 35 USC 103(a) at pages 14-16 of the office action dated 02/15/2005. Capecchi did not teach use of the lacZ gene as required by claim 48 and therefore the rejection is withdrawn in favor of the new rejection below.

Claims 37,41 and 43-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour [**Development**, 117:13-28 (1993)] in view of Tornetta (1997, J. Immunol., Vol. 158, pages 5277-5282).

The claims 43-48 are directed to a transgenic mouse comprising a disruption in an anaphylatoxin C3a receptor gene, claim 41 is directed to a method of making said mouse using a mouse ES cell introduced into a mouse blastocyst and cells or tissues derived therefrom the mouse (claim 37). Claims 34-36 are not included in this rejection as they include phenotypic limitations that are not predictable based on the prior art of record.

Mansour taught transforming a mouse ES cell with a nucleic acid construct targeting the int-2 gene, resulting in an inactivating (null; see abstract and page 23, paragraph 3) insertion of a selective marker gene into the endogenous int-2 locus (page 14, col. 1, paragraph 3), and using said cell to generate a mouse whose genome comprises a disruption in the int-2 gene (for specific method steps see page 15, col. 2, paragraph 3). The targeting construct comprised both a neo resistance gene and a visible lacZ marker (page 14, col. 1, paragraph 3). Mansour differs from the claimed invention in that the targeting construct does not disrupt the anaphylatoxin C3a receptor gene.

However, at the time the claimed invention was made, Tornetta taught the cloning of the mouse anaphylatoxin C3a receptor gene (entire document and for further sequence detail GenBank Accession No. U77461).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Mansour wherein the gene was the anaphylatoxin C3a receptor gene as taught by Tornetta. One of ordinary skill in the art would have been sufficiently motivated to replace theint-2 gene with the anaphylatoxin C3a receptor gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the anaphylatoxin C3a receptor gene to determine its role in inflammatory disease, as described by Tornetta (page 5277, column 2, lines 3-8). Tornetta further supports the motivation to generate a transgenic mouse comprising a disruption in the anaphylatoxin C3a receptor gene based on the success of a similar disruption in the anaphylatoxin C5a receptor gene substantiating a role of the anaphylatoxin C5a receptor gene in inflammatory disease (Tornetta, page 5277, column 1, last 2 lines-column 2 lines 1-3).

The skilled artisan would have a reasonable expectation of success in combining the teachings of Mansour and Tournetta because it was routine in the art to knock out any desired gene to determine the phenotypic effects of a specific gene disruption.

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Valarie Bertoglio
Examiner
Art Unit 1632

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER